REMARKS

Claims 14 and 40 remain before the Examiner for reconsideration. Claims 1-13 and 15-39 have been canceled without prejudice.

In the Office Action dated May 17, 2005, the Examiner rejected claims 14-25, 27-40 under 35 U.S.C. 112, first paragraph, "as failing to comply with the written description requirement." Specifically, the Examiner asserted that:

> The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.
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> A. The choices of Rl or R2 as haloalkyl appears to be new matter. Where are such groups specifically described in the specification? Applicants point to page 7, but halo is not listed as a substituent.
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> B. The two provisos are clearly new; they both lack description. One requires that at least one of the variables R1, R2, R3 or R4 have a choice drawn from a certain list of 5 choices. The second says that at least one other of those same variables be NOT drawn from a list of two variables. Even a negative limitation requires description, Ex Parte Grasselli, 231 USPQ 393. The concept of the definition of these variables depending on each other is entirely new. The traverse is unpersuasive. Applicants cite Ex parte Parks, 30 USPQ 1234, 1236, but that case is not inconsistent with either Grasselli or the examiner's position. In Parks, the Board of Patent Appeals and Interferences held, in effect, that the precise limitation was effectively described in the specification even though the exact words were not present. That is not the case here. It is not the case that 'the disclosed specification conveyed to a skilled artisan that' e.g. there are any such requirements. The specification has these variables are all being independent of each other; see e.g. page 5, line 14. Now, the definition of e.g. Rl depends on the definition of the other three. That is the new concept. Applicants then discuss some hypothetical claims, but these are not under prosecution here.

Applicants respectfully traverse the Examiner's rejection. Nonetheless, in the interest of expedient prosecution, Applicants have amended the claims to set forth a specific embodiment of the present invention, thereby obviating the Examiner's rejection. Applicants reserve the right to reassert the previously claimed subject matter.

The Examiner also rejected Claims 14-40 are rejected under 35 U.S.C. 112, first

paragraph, as failing to comply with the enablement requirement." Specifically, the Examiner asserted that:

> The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.
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> Pursuant to In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), one considers the following factors to determine whether undue experimentation is required: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure. Some experimentation is not fatal; the issue is whether the amount of experimentation is "undue"; see In re Vaeck, 20 USPQ2d 1438, 1444.
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> The analysis is as follows:
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> (1) Breadth of claims.
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> (a) Scope of the compounds. This varies according to claim. Claim 14, because of the substantial scope of the 8 primary variables, covers billions of compounds. Claims 26, 29 and 30 cover only a few species; claims 39-40 cover single species.
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> (b) Scope of the diseases covered. The coverage is immense. These cover very broad ranges of cancers. Some examples:
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> A. Malignant Melanoma is a malignancy of melanocytes, and occurs most commonly in the skin, but can also appear beneath the nail plate, in the eyes, ears, GI tract, leptomeninges of the central nervous system, and oral and genital mucous membranes. There are 4 major types: superficial spreading, nodular, lentigo maligna, and acral lentiginous melanoma. There are a number of uncommon forms as well: Desmoplastic/neurotropic melanoma, Mucosal (lentiginous) melanoma, Malignant blue nevus, Melanoma arising in a giant congenital nevus, and Melanoma of soft parts (a kind of clear cell sarcoma). In addition, there are Amelanotic melanomas, which are nonpigmented.
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> B. There are several main types of stomach cancers, which are very different from each other. (1) Lymphomas of the stomach are cancers of the immune system tissue that are found in the wall of the stomach. These come in two main categories. One is the Non-Hodgkin's lymphomas of the stomach, including MALT lymphoma, and assorted Large Cell Lymphoma of the Stomach such as anaplastic CD30 (Ki-1) positive large cell lymphoma (ALCL). The other is Hodgkin Lymphoma in the Stomach. These include both lymphomas which are primary to the stomach, and nodal lymphomas that have spread to the stomach

from e.g. the spleen or liver and are thus secondary. There are Tertiary gastric lymphomas as well. (2) Gastric stromal tumors (GISTs) develop from the tissue of the stomach wall. There are an assortments of these; GISTs vary from cellular spindle cell tumors to epithelioid and pleomorphic ones. (3) Carcinoid tumors are tumors of hormone-producing cells of the stomach. These are classified into are classified into those that are associated with hypergastrinemic states (type 1, atrophic gastritis, pernicious anemia); Zollinger-Ellison syndrome EZESI tumors (type 2), and tumors without hypergastrinemia (type 3 or sporadic). (4) Carcinoma of the Stomach exists in five types: papillary, tubular, mucinous, signet-ring cell adenocarcinoma and undifferentiated carcinoma. (5) Soft tissue sarcomas, most notably leiomyosarcoma of the stomach. There are other tumors as well, including Gastric Lipoma, gastric xanthelasma, and benign reactive lymphoid hyperplasia (pseudolymphoma).

C. There are many types of colon cancers, and this category is rather diverse. Most are adenocarcinomas, either of the mucinous (colloid) type or the signet ring type. Less common colon cancers include squamous cell, neuroendocrine carcinomas, carcinomas of the scirrhous type, lymphomas, melanomas, sarcomas (including fibrosarcomas and Leiomyosarcomas), and Carcinoid tumors. Because these are fundamentally different types of tumors, their treatment greatly differs, although adenocarcinomas and squamous cell tend to be treated the same.

D. Leukemia is any malignant neoplasm of the blood-forming tissues. Leukemia can arise from many different sources. These includes viruses such as EBV, which causes Burkitt's lymphoma, and HTLV-1, linked to certain T cell leukemias. Others are linked to genetic disorders, such as Fanconi's anemia, which is a familial disorder, and Down's Syndrome. Other leukemias are caused by exposure to carcinogens such as benzene, and some are actually caused by treatment with other neoplastic agents. Still other leukemias arise from ionizing radiation, and many are idiopathic. Leukemias also differ greatly in the morphology, degree of differentiation, body location (e.g. bone marrow, lymphoid organs, etc.) There are dozens of leukemias. There are B-Cell Neoplasms such as B-cell prolymphocytic leukemia and Hairy cell leukemia. There are T-Cell Neoplasms such as T-cell prolymphocytic leukemia, aggressive NK cell leukemia, and T-cell granular Lymphocytic leukemia. There are different kinds of acute myeloid leukemias, acute promyelocytic leukemias, acute myelomonocytic leukemia, chronic myelomonocytic leukemia, acute monocytic leukemias, and erythroleukemias. There is also acute megakaryoblastic leukemia, acute promyelocytic leukemia, Multiple Myeloma, lymphoblastic leukemia, hypocellular acute myeloid leukemia, Ph-BCR- myeloid leukemia, acute basophilic leukemia, acute myleofibrosis, chronic granulocytic leukemia, chronic neutrophilic leukemia, chronic eosinophilic leukemia and many others.

E. The main types of lung cancer are small cell (oat cell), Giant Cell Carcinoma, clear cell, adenocarcinoma of the lung, squamous cell cancer of the lung, mesothelioma and Large Cell Carcinoma (a default category of any lung tumor

that cannot be otherwise classified).

(2) The nature of the invention and predictability in the art: The invention is directed toward medicine and is therefore physiological in nature. It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved," and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher,* 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

(3) Direction or Guidance: That provided is deficient. The daily dosage range information was omitted from the specification.

(4) State of the Prior Art: The claimed compounds are camptothecins. No camptothecin has ever been found to be effective against any of these categories generally.

(5) Working Examples: No actual working examples for the treatment of cancer are presented. Data appears for 3 cell lines, one of which (833K) is a testicular cell line, not a cancer type listed. However, one cell line cannot possible demonstrate leukemia generally, and one cannot demonstrate lung generally, given the huge diversity of leukemias and lung cancers.

(6) Skill of those in the art: The prior art knows that there never has been a compound capable of treating cancer generally. There are compounds that treat a modest range of cancers, but no one has ever been able to figure out how to get a compound to be effective against cancer generally, or even a majority of cancers. Thus, the existence of such a "silver bullet" is contrary to our present understanding in oncology. Even the most broadly effective antitumor agents are only effective against a small fraction of the vast number of different cancers known. This is true in part because cancers arise from a wide variety of sources, such as viruses (e.g. EBV, HHV-8, and HTLV-1), exposure to chemicals such as tobacco tars, genetic disorders, ionizing radiation, and a wide variety of failures of the body's cell growth regulatory mechanisms. Different types of cancers affect different organs and have different methods of growth and harm to the body, and different vulnerabilities. Even those that affect just a single organ are often not generally treatable. Since it is beyond the skill of oncologists today to get an agent to be effective against cancers generally, evidence that the level of skill in this art is low relative to the difficulty of such a task. The skill thus depends on the particular cancer involved. There are cancers where the skill level is high and there are multiple successful chemotherapeutic treatments. In many, many cancers, however, there is no chemotherapy whatsoever available. No compound has ever been found effective generally against leukemias, lung cancers, melanomas, etc because they are simply too diverse. Lymphomas of the stomach are not commonly treated with ordinary anti-cancer agents, but instead, surgery or radiation or antibiotic therapy(e.g. amoxicillin, metronidazole, bismuth, omeprazole) are the Primary Treatments. Treatment of malignant melanoma is normally with surgery or biological agents. Chemotherapy with non-biologics has

a very limited role. The majority of common cancers do not respond to chemotherapy.

(7) The quantity of experimentation needed: Given the fact that historically the development of new cancers drugs has been difficult and time consuming, and especially in view of factors 1 and 6, the quantity of experimentation needed is expected to be great.

MPEP 2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright,* 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here.

The traverse is unpersuasive. Applicants make a broad statement about what "camptothecin analogs" do, but this is simply not true in terms of the actual scope of this claim. Where is there evidence for example that such compounds are effective against e.g. lymphomas of the stomach, squamous cell cancer of the colon, hairy cell leukemia , or mesothelioma of the lung? With regard to the dosage, applicants point to page 10, but this simply gives the size of a dose, not a daily or weekly dosage. Thus, one does not know whether this dose is to be given, say, once a week or given e.g. 4 times a day. Applicants refer in this regard to FDA approval, but the PTO is not concerned with that; merely with what the specification actually teaches.

Applicants respectfully traverse the Examiner's rejection. Once again, in the interest of expedient prosecution, Applicants have amended the claims to set forth a specific embodiment of the present invention, thereby obviating the Examiner's rejection. Applicants reserve the right to reassert the previously claimed subject matter. Applicants note that the claims as amended set forth the subject matter of claims 39 and 40 that the Examiner indicated to be allowable in the Office Action dated September 30, 2004.

In view of the above amendments and remarks, the Applicants respectfully requests that the Examiner, indicate the allowability of the Claims, and arrange for an official Notice of Allowance to be issued in due course.

Respectfully submitted,

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